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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/445,193	12/02/1999	SHIGENORI OHKAWA	2470US0P	9630

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TAKEDA PHARMACEUTICALS NORTH AMERICA, INC
INTELLECTUAL PROPERTY DEPARTMENT
475 HALF DAY ROAD
SUITE 500
LINCOLNSHIRE, IL 60069

EXAMINER	
ROBINSON, BINTA M	

ART UNIT	PAPER NUMBER
1625	

DATE MAILED: 05/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/445,193	OHKAWA ET AL.	
	Examiner	Art Unit	
	Binta M. Robinson	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-15,22,24-26 and 28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-13,15,22,24-26 and 28* is/are rejected.

7)☒ Claim(s) *14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Claims 11, 12, 13, 14, 15, 22, 24 25, 26, 28, are pending.

The 112, first paragraph rejection of claim 14, the 112, second paragraph rejection of claim 12 made at paper no. 21 are withdrawn in light of applicant's comments filed 1/28/04. Claims 13-15, 22, 24, and 25-26 which were said to be previously allowable at paper no. 21 have not been found to be allowable in this action and have been either rejected or objected to below.

(old rejection)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim(s) 25 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claim 25, lines 8-9, page 6 of the paper filed 1/28/04, the phrase "which hydrocarbon group is optionally further substituted" is indefinite. The hydrocarbon group can already be optionally substituted by an aromatic group. What else can the hydrocarbon group be substituted with and where is the substitution on the hydrocarbon?

(new rejections)

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11

F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 11, 12, 13, 15, 22, and 24 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10, 19, 20, 21, 26, 27, 28, 33 of copending Application No. 2004/0034049. Although the conflicting claims are not identical, they are not patentably distinct from each other because the US patent application teaches a genus that encompasses the subgenus of the instant claims.

US Patent Application 2004/0034049 et. al. teaches the instant compound as shown in Formula I, where R1 and R2 are an optionally substituted hydrocarbon group or R1 and R2 may be taken together with the adjacent carbon atom to form an optionally substituted 3 to 8-membered heterocyclic ring, R3 is an optionally substituted heterocyclic group, R4c-X- wherein R4c is an optionally substituted aliphatic hydrocarbon group or an acyl group, X is an oxygen atom, Y is an oxygen atom, Ring C is a benzene ring or a prodrug thereof. At columns 1-2, see formula I and the radicals defined. The difference between the prior art compound and the instantly claimed compounds is the teaching of a generic compound versus a disclosed species. It would have been obvious to one of ordinary skill in the art to select various known radicals

within a genus to prepare structurally similar compounds. For instance, see the compound, 3-(4-isopropylphenyl)-2,4,6,7-tetramethylbenzofurna-5-yl 4-methoxy benzoate, where a disclosed species is exemplified. Accordingly, the compounds are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds over those of the generic prior art compounds.

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22 and 25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. A method for suppressing Beta-amyloid toxicity in a mammal which comprises administering to said mammal an effective amount of the instant compound of the formula I is not a method of treating a disease, but a method of treating a mechanism. The disease being treated by this stimulation is not being stated. The suppression of beta-amyloid toxicity must be related to a disease that needs to be improved and this disease needs to be recited.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The Nature of the Invention

The nature of the invention is that the compounds of the instant claims and their production and use in suppressing toxicities caused by beta-amyloid protein.

State of the Prior Art

Neurodegerative diseases are progressive disorders that cause fatal damage to cells or nerve cell death. As principal neurodegenerative diseases, known are Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's chorea, peripheral nervous system disorders such as typically diabetic neuropathy. Most of those are related to aging, and in fact cases that present the symptoms of those diseases increase with aging. However, middle-aged and even young cases may often present the symptoms of those diseases.

A current medication therapy mainly employs a substitution therapy that compensates for the depletion of neurotransmitters accompanying neurodegeneration. A dopaminergic agent such as L-dopa which is a precursor of dopamine is employed to

treat Parkinson's disease, while an acetylcholine decomposition enzyme inhibitor is employed to treat Alzheimer's disease, the both being used as a substitution therapy agent or a symptomatic therapy agent. However, such a substitution therapy agent or a symptomatic therapy agent does not suppress the progress of neurodegeneration, and its effect becomes attenuated gradually with progression of the disease. A benzofuran derivative that has an activity for promoting the regeneration of a nerve and is useful as a prophylactic and therapeutic agent against a neurodegenerative disease is disclosed in WO 98/55454 and WO 00/34262.

The Predictability or lack thereof in the art

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to therapeutic effects of amyloid toxicity-associated diseases, whether the amyloid toxicity was reduced, or unaffected, or increased would affect the possible treatment of any disease.

Hence, in the absence of a showing of correlation between all the diseases claimed as capable of treatment by the compound of claim 1 and the reduction of amyloid toxicity, one of skill in the art is unable to fully predict possible results from the administration of the compound of claim 1 due to the unpredictability of the role of

amyloid toxicity in the treatment of these diseases, i.e. whether promotion or inhibition would be beneficial for the treatment of the diseases.

The nature of pharmaceutical arts is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

Cell protecting activity ranges from 30.7 % to 47 %. There are significant differences in cell protecting activity for small changes in structure. For example, compounds 1 and 25 on pages 103 and 104, differ at the moiety. For compound 1, e is benzyloxy; for compound 25, the e moiety is benzylmethoxy. However, the cell protecting activity for compound 1 is 30.7 % and for compound 25 is 47%. The level of predictability regarding cell protecting activity is low.

The amount of direction or guidance present

The various compounds have not been tested for
their affects on the various disease claimed in claim 26, 28. The direction present in the instant specification is that the compounds of claim 1 can inhibit the production of suppress amyloid toxicity which helps in the Alzheimer's disease. However, the specification is silent and fails to provide guidance as to whether the diseases listed as amyloid toxicity-mediated diseases, require the suppression of amyloid toxicity.

The breadth of the claims

The breadth of the claims is that the compound of claim 1 can suppress amyloid toxicity and can treat Alzheimer's disease.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what listed diseases would be benefited by the suppression of amyloid toxicity and would furthermore then have to determine whether the claimed compounds would provide treatment of the disease by the suppression of amyloid toxicity.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compound of the claim 1 for the suppression of amyloid toxicity. As a result necessitating one of skill to perform an exhaustive search for which diseases mediated by amyloid toxicity- can be treated by the compound of claim 1 in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that " a patent is not a hunting license. It is not a reward for search , but compensation for its

successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which amyloid toxicity-mediated diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 26 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 26 recites the limitation "a method for treating Alzheimer's disease" in line 2 of page 6. There is insufficient antecedent basis for this limitation in the claim.

B. Claim 28 recites the limitation " method for treating Alzheimer's disease" in line 2 of page 6. There is insufficient antecedent basis for this limitation in the claim. Claim 14 is objected to because it is based on a rejected claim.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Binta M. Robinson whose telephone number is (571) 272-0692. The examiner can normally be reached on M-F (9:30-6:00).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 11-15, 22, 24-26, 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Terao CA 109 in view of Friebe CA 100.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Ascertain the teaching of the prior art

Terao disclosed similar benzofuranyl compounds that are antiallergic agents (see Terao CA 109 and structural delineation of compounds).

The difference between the art and the claim

Terao et al. CA 109 disclosed all the elements of the claims **except** the phenyl ring of the benzufuranyl bicyclic system is substituted with methyl while the instant claims are hydrogen. Friebe et al. CA 100 disclosed structurally similar benzofuranyl antiallergic compounds which explicitly exemplified that a lower alkyl substitution on the phenyl ring of benzofuranyl bicyclic system is an optional choice for such compounds.

Rational for finding prima facie obviousness

Terao and Friebe are analogous art in benzofuranyl antiallergic compounds. An ordinary skilled person in the art in possession of the above references would find the claims prima facie obvious **because** the claims differ from the Terao reference in the replacement of hydrogen atoms of a ring with a methyl group. The replacement of a hydrogen with a methyl group is normally within the sphere of prima facie obviousness that surrounds the known compound. In re Wood 199 USPQ 137. In the instant case, one would be suggested and motivated by the reasonable operability disclosed by Friebe that substitution or nonsubstitution on the phenyl ring of the bicyclic system would not interfere with the therapeutic function of such class of compounds.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699.

A facsimile center has been established. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703)308-4242, (703)305-3592, and (703)305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)-272-1600.

BMR

JOSEPH K. McKANE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600